Abstract:

Purpose: To summarize the surface contamination levels of five commonly used hazardous drugs in hospital pharmacies, identifying practice patterns associated with contamination.

Methods: Contamination testing data was compiled to evaluate surface contaminants of five hazardous drugs (docetaxel, paclitaxel, cyclophosphamide, ifosfamide, and 5-fluorourcil). Data from 799 wipe events over 6 years was collected from 338 hospital pharmacies. The contamination level for each drug was categorized as non-detectable (ND; $\leq$ 10 ng/ft^2), low (between 10 and $\leq$ 100ng/ft^2), medium (between 100 and $\leq$ 1,000ng/ft^2) or high (> 1,000ng/ft^2). Surface exposures for each drug were summarized based on location, contamination at first and subsequent wipe events, and the use of a closed system transfer device (CSTD).

Results: The majority of contamination results corresponded to locations at or near hazardous drug preparation, but also occurred in areas were hazardous drug was not prepared. There was a higher incidence of contamination levels (high, medium, and low, respectively) at first wipe event (10.2%, 17.4%, and 17.7%) compared to subsequent wipe events (5.8%, 12.2%, and 13.6%) (P<0.0001). There was a lower incidence of contamination levels at institutions that used CSTDs (6.3%, 12.8%, and 14.4%) compared to institutions that did not use CSTDs (14.2%, 17.9%, and 17.3%) (P<0.0001).

Conclusions: The majority of highest contamination levels corresponded to locations where hazardous drugs were prepared. While the incidence of contamination was lower at subsequent wipe events and at institutions that used CSTDs, contamination was not completely eliminated in either scenario, suggesting that routine contamination testing is beneficial in recognizing and correcting practices that lead to surface exposures.

Introduction:

Hazardous drugs are known to be harmful to both healthy and cancerous cells. The mechanism of action of hazardous drugs involves interference with cellular synthesis, providing therapeutic benefits in cancer patients, but potential harm to healthy human cells.[1] The doses at which hazardous drugs provide therapeutic benefit have been well studied and are reflected in FDA approved dosing of these agents. One element that is often overlooked however is the health and safety of the healthcare workers that prepare and administer hazardous drugs, most notably pharmacy and nursing personnel.

The recognition of occupational exposure to hazardous drugs can be traced back to the late 1970s when biologic monitoring revealed contamination exposure in nurses who handled hazardous medications.[2] Since then, many studies have documented occupational hazardous drug exposures and the resulting adverse effects including mutagenicity and reproductive effects.[3-14] In 2004, the National Institute for Occupational Safety and Health (NIOSH) released an alert statement for preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. This report specifically detailed that working with or near hazardous drugs in a healthcare setting can lead to adverse effects such as skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.[15] After recognizing this contamination and the health risks associated with occupational exposure, the healthcare community worked towards implementing various measures to minimize exposure to hazardous drugs. In this effort, groups including NIOSH, the American Society of Health-System Pharmacists (ASHP), and the International Society of Oncology Pharmacy Practitioners (ISOPP) have published guidelines addressing the safe handling of hazardous drugs.[15-17] Interventions included in these guidelines were implementing vertical laminar airflow biological safety cabinets, providing personal

protective equipment (PPE) to workers, introducing closed-system transfer devices (CSTDs) to hazardous drug preparation and administration, and providing routine medical surveillance measures for staff. While each of these methods have reduced occupational exposure to hazardous drugs to some extent, surface contamination is still a prevalent concern in hospital pharmacies and nursing units,[18-23] especially in regards to surface contamination on the outside of hazardous drug vials.[24-28]

The new USP <800> guidelines add additional information to USP <797> and provides workplace standards to protect personnel when handling hazardous drugs. USP <800> recommends that environmental wipe sampling for hazardous drug surface residue be performed every six months to evaluate for presence of contamination.[29] While USP <800> gives recommendations for frequency of contamination testing, it does not provide any guidance on how extensive the testing should be, including how many locations or how many drugs should be tested. Routine monitoring of contamination studies is crucial in allowing institutions to be proactive in minimizing hazardous drug contamination. While a site does not want to under-monitor and risk missing evidence of contamination, it also does not want to over-monitor and waste resources. Several studies have reported contamination exposures with and without the use of a CSTD[30-33]; however, no studies to our knowledge have reported additional important characteristics of hazardous drug surface contamination including the locations associated with higher contamination levels and the incidence of contamination at first wipe event compared to subsequent wipe events.

The objective of this study is to summarize the surface contamination levels of five commonly used hazardous drugs (docetaxel, paclitaxel, cyclophosphamide, ifosfamide, and 5-fluorourcil) in hospital pharmacies. This study also summarizes the locations that correspond

with the highest contamination levels, the incidence of contamination at first wipe event compared to subsequent wipe test events, and the incidence of contamination at institutions that use CTSDs compared to those that do not use CSTDs.

Methods:

The hazardous drug surface exposure analysis was performed using ChemoGLO™ (Chapel Hill, NC) hazardous drug contamination wipe kits, which analyzes and quantifies the amount of surface contaminants of hazardous drugs including docetaxel, methotrexate, cyclophosphamide, ifosfamide, 5-FU, paclitaxel, and platinum analogues (e.g. cisplatin, carboplatin, and oxaliplatin). Detailed methods for wipe sampling and analyses of wipe samples have been published previously.[34]

This study retrospectively evaluated 6 years (from August 2009 to June 2015) of wipe data collected in 338 pharmacies from separate healthcare institutions to evaluate patterns and characteristics associated with hazardous drug surface exposure. This study focused on the most commonly tested drugs: docetaxel, paclitaxel, cyclophosphamide, ifosfamide, and 5-fluorourcil. A "wipe event" was defined as each time an institution ordered and performed a wipe study and then sent the wipe samples to the lab for analysis.

For each wipe event, the institution filled out a data collection sheet, indicating the number of drugs and locations to be tested. The majority of institutions chose to test for 5 different drugs at 6 different locations. The data collection sheet also gathered site-specific practices, such as the time of day the site performed the wipe testing, whether the area was cleaned prior to testing, and the use of CSTDs.

Data from 799 different wipe events were included in this study. The highest contamination results for each drug among the locations tested were used to summarize the surface contamination. Contamination results from the 799 wipe events were categorized into either first wipe event or subsequent wipe events. The first wipe event was defined as the first time in which an institution ordered and performed a wipe test. Subsequent wipe events were defined as any wipe event that occurred at the same institution greater than four weeks after a previous wipe event (separate wipe studies are normally performed every one, three or six months). The contamination level for each drug at each location was defined as non-detectable (ND); ≤ 10 ng/ft^2 (≤ 0.0108 ng/cm^2), low; between 10 and ≤ 100 ng/ft^2 (between 0.0108 and 0.108 ng/cm^2), medium; between 100 and $\leq 1{,}000$ ng/ft^2 (between 0.108 and 1.08 ng/cm^2), or high; $> 1{,}000$ ng/ft^2 (> 1.08 ng/cm^2). Factors evaluated included the locations corresponding to highest contamination levels for each drug at each site, incidence of contamination levels at first wipe event compared to subsequent wipe events, and incidence of contamination at institutions that reported use of a CSTD compared to those who did not use a CSTD.

The Cochran-Armitage Trend Test was performed to evaluate the association between overall contamination at subsequent wipe events compared to first wipe event and the association between overall contamination at institutions that used CSTDs compared to institutions that did not use CSTDs.

Results:

This study evaluated 799 total wipe events, which consisted of 5,842 individual wipe samples. The results included 338 unique healthcare institutions that completed at least one wipe event, with 39.64% of these unique institutions completing a subsequent wipe event. The

healthcare institutions that completed at least one wipe event represent diverse geographical regions within the United States (20.40% Southwestern region; 16.65% Southeastern region; 13.14% Northeastern region; 29.91% Midwestern region; 18.65% Western region; and 1.25% outside of the US). Participating sites reported the time of day the wipe event was performed (29.66% reported at the start of the work day; 38.17% reported in the middle of the work day; 20.28% reported at the end of the work day; and 11.89% did not include information). Sites also reported whether the surface tested was cleaned prior to wipe sampling (13.52% reported cleaning prior to wipe sampling; 75.09% reported no cleaning prior to wipe sampling; and 11.39% did not include information). Participating sites were also asked to report whether or not CSTDs were used in hazardous drug preparation (75.47% reported using CSTDs; 17.40% reported not using CSTDs; and 7.13% did not include information).

Pharmacy locations corresponding with highest contamination levels

Each institution self-reported on the wipe kit data collection sheet the location in which each wipe was performed. All reported locations were categorized into 6 different groupings: airfoil, floor below a biologic safety cabinet (BSC), BSC surfaces, pharmacy surfaces (not including BSC), floor of the pharmacy (not directly under BSC), and miscellaneous items (including phones, keyboards, or chemo transportation bins in the pharmacy). The locations corresponding with the highest detected contamination level for each drug per wipe event are summarized in **Table 1**. The majority of the highest contamination results corresponded to locations at or near hazardous drug compounding (25.88% airfoil, 22.28% floor below BSC, and 25.96% at BSC surfaces) with the remaining 25.88% of highest contamination results corresponding to areas not located near hazardous drug compounding (12.6% pharmacy surfaces

(not including BSC surfaces), 3.9% floors in pharmacy (not under BSC), and 9.4% miscellaneous items).

Incidences of contamination for each drug at first and subsequent wipe events

The contamination results for each drug from each wipe event were analyzed and categorized into either first wipe event or subsequent wipe events. The incidence of contamination for each drug at first and subsequent wipe events is summarized in **Table 2**. The incidence of wipe results with high, medium, or low contamination was less on subsequent wipe events compared to first wipe event, with the exception of the ifosfamide high contamination results. There was a lower incidence of high contamination for ifosfamide on first wipe event compared to subsequent wipe events (5.84% and 6.61%, respectively). The incidence of wipe results with non-detectable contamination was higher for each drug on subsequent wipe events compared to first wipe event. The overall incidence of contamination levels (compiling high, medium, and low levels) for all drugs was lower at subsequent wipe events compared with first wipe event ($Z = -8.47$; $P < 0.0001$).

Incidence of contamination for each drug in relation to CSTD use

Based on institutional practices indicated on the wipe kit data collection sheet, all wipe results for each of the 5 drugs tested were stratified into either CSTD users or CSTD non-users. For CSTD users, the incidence of various contamination levels for each drug was quantified. The same was done for CSTD non-users and the incidence of contamination was compared between CSTD users and CSTD non-users. The results are summarized in **Table 3**. There was a higher incidence of high, medium, or low contamination results in the CSTD non-user's category

compared to CSTD users, with the exception of 5-FU low contamination results. The 5-FU contamination results had equal incidence of low contamination results between CSTD users and non-users (12.88%). There was a higher incidence of non-detectable contamination results in the CSTD user's category compared to CSTD non-users. However, as depicted in the results there was still low, medium and high levels of exposures of all drugs even with the use of a CSTD (14.37%, 12.84%, and 6.30%, respectively). The overall incidence of contamination levels (compiling high, medium, and low levels) for all drugs was higher for CSTD non-users compared to CSTD users ($Z = 8.73$; $P < 0.0001$).

Discussion:

The data summaries in this study showed that there is a high variability in the surface exposures of hazardous drugs in pharmacies. The majority of the highest contamination results corresponded to locations where hazardous drugs were prepared. A higher incidence of contamination was identified at first wipe event compared to subsequent wipe events ($P < 0.0001$). Additionally, a higher incidence of high, medium, and low contamination levels was detected at institutions that did not use CSTDs compared to institutions that did use these devices ($P < 0.0001$).

The contamination results stratified by location are consistent with previous contamination results published in the literature showing that surface contamination can be found at the site of compounding as well as other locations throughout the pharmacy.[18-20] While the majority of highest contamination results in this study corresponded to locations involved in the preparation of hazardous drugs, it is important to note that the choice of locations tested was at the discretion of the institution, and that an institution may have tested locations involved in hazardous drug

preparation more frequently. It is also important to note that contamination still exists in other areas of the pharmacy not directly involved in compounding (i.e. floors not beneath the BSC, pharmacist checking counters, and phones or keyboards). The awareness that contamination exposures are occurring at locations at or near the preparation of hazardous drugs suggests that additional measures should be taken at these sites to decrease contamination during the preparation process, but efforts should not exclude other areas throughout the pharmacy.

The difference in incidence of contamination between results at first wipe event and subsequent wipe events suggests that monitoring is beneficial in recognizing and correcting practices that lead to surface exposures. Contamination was not completely eliminated at subsequent wipe events, suggesting that continued monitoring is required with the inclusion of additional or different strategies to reduce exposure. Hazardous drug contamination wipe studies can be performed before and after a change in compounding practice or a change in protective measures in a hospital, which allows an institution to quantify the impact the intervention made in reducing contamination levels. The ultimate goal is non-detectable levels of contamination in each wipe throughout the pharmacy and institution. Thus, hospitals need to continue monitoring surface exposures to evaluate if they are maintaining best practices in order to keep contamination levels at a minimum.

The practice of repeated surface contamination testing is consistent with the recommendations in USP <800> that testing should be performed routinely (at baseline and then at least every 6 months, or more frequently if needed) to confirm containment of the contamination.[29] While USP <800> does not detail the locations or number of drugs that should be tested, the data presented here supports testing a variety of drugs and locations within the pharmacy (locations directly and non-directly involved in hazardous drug preparation) for

hazardous drugs that are compounded most often at that institution. The majority of institutions chose to test six different locations for the five most commonly utilized chemotherapies at their institution. Until further research suggests otherwise, the data from this study supports testing a minimum of 5 drugs at 6 different locations to get an accurate summary of overall contamination levels within a hospital pharmacy.

One method in decreasing hazardous drug exposure during preparation is the use of a CSTD.[23, 30-33] The data from this study showed a lower incidence of contamination at institutions that used CSTDs in the preparation process. It is important to note that low, medium, and high contamination levels still existed at institutions using CSTDs, suggesting that the use of a CSTD did not completely remove or prevent all exposures. The additional use of cleaning products in the preparation areas before and after the use of CSTDs addresses both of these issues.[34] The lower incidence of contamination at institutions that reported use of CSTDs supports the USP <800> recommendation to use CSTDs as an adjunctive protection method in preparation and administration of hazardous drugs.[29]

While the desired goal is to have no surface contamination (non-detectable), it should be evident that this is not achieved in all situations and there is a high variability in surface exposures of hazardous drugs in pharmacies. Even at institutions where best practices are implemented, the data in this study shows that surface contamination was detectable in variable and unpredictable levels. The reasons for this are unclear but may include spills or breaking of a vial, not implementing all best practices, inconsistent use of safety practices and PPE, variability in the appropriate use of CSTDs, the ability of the CSTD to be truly closed, and external contamination of hazardous drug vials from the manufacturer.[24-28,35] So while non-detectable

contamination is not always possible, routine contamination testing is useful in identifying areas of contamination and implementing changes to prevent future contamination.

A limitation of this study was the exclusion of contamination results from nursing and drug administration areas. The 2004 NIOSH Alert detailed that occupational exposure to hazardous drugs can occur at many points in the medication use process from procurement of the drugs to administration of drugs to patients.[15] However, the focus of this study was on pharmacy practice patterns and the incidence of exposures of hazardous drugs. Future research and studies in other areas, such as nursing and administration areas, are needed. In regards to pharmacy-specific practices, additional characteristics that should be evalulated in future studies include the volume of chemotherapy prepartaions at each institution daily, which CSTD was used, whether CSTDs were used in all preparations including 5-Fluorouracil pumps, the level of experience of staff compounding the hazardous drugs, and the cleaning processes within the pharmacies.

Conclusions:

To date this is the largest study evaluating pharmacy practices and characteristics associated with levels of hazardous drug surface contamination. The highest contamination results occurred at locations both directly and indirectly involved in hazardous drug compounding, suggesting drug exposures can travel throughout the pharmacy. A higher incidence of contamination was identified at first wipe event compared to subsequent wipe events, suggesting that monitoring is beneficial in recognizing and correcting practices that lead to hazardous drug surface exposures. Contaminations were not completely eliminated at subsequent wipe events, suggesting that continued monitoring is required with the inclusion of additional or different strategies to reduce exposures. A higher incidence of high, medium, and low contamination levels was detected at

institutions that did not use a CSTD compared to institutions that did use these devices. However, the use of a CSTD did not completely prevent all exposures, further suggesting that multiple practices, such as combining a CSTD with a cleaning product, should be implemented in hazardous drug preparation areas to reduce and prevent exposures.

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Table 1: Occurance of pharmacy locations with highest drug contamination levels						
Drug	**Number of Contaminations (% Contamination by Pharmacy Location)**					
	Airfoil	**Floor Below BSC**	**BSC Surfaces**	**Pharmacy Surfaces (not BSC)**	**Floor Pharmacy**	**Misc. Items**
Paclitaxel (n = 211)	56 (26.54%)	42 (19.91%)	62 (29.38%)	19 (9.00%)	12 (5.69%)	20 (9.48%)
Docetaxel (n = 166)	31 (18.67%)	38 (22.89%)	30 (18.07%)	38 (22.89%)	9 (5.42%)	20 (12.05%)
Cyclophosphamide (n = 325)	82 (25.23%)	91 (28.00%)	86 (26.46%)	32 (9.85%)	14 (4.31%)	20 (6.15%)
Ifosfamide	65	45	52	19	2	13

(n = 196)	(33.16%)	(22.96%)	(26.53%)	(9.69%)	(1.02%)	(6.63%)
5-FU (n = 296)	75 (25.34%)	50 (16.89%)	80 (27.03%)	42 (14.19%)	10 (3.38%)	39 (13.18%)
Overall for all drugs (n = 1194)	309 (25.88%)	266 (22.28%)	310 (25.96%)	150 (12.56%)	47 (3.94%)	112 (9.38%)

Table 2: Incidence of contamination for each drug at first and subsequent wipe events								
Drug	**High Contamination[A]**		**Medium Contamination[B]**		**Low Contamination[C]**		**Non-detectable Contamination[D]**	
	1st Wipes	**Subsequent Wipes**	**1st Wipes**	**Subsequent Wipes**	**1st Wipes**	**Subsequent Wipes**	**1st Wipes**	**Subsequent Wipes**
Paclitaxel 1st wipe (n = 336) Subsequent (n = 460)	4.76%	1.96%	18.45%	8.70%	21.13%	16.96%	55.65%	72.39%
Docetaxel 1st wipe (n = 336) Subsequent (n = 460)	3.27%	1.30%	14.58%	5.65%	17.26%	10.22%	64.88%	82.83%
Cyclophosphamide 1st wipe (n = 293) Subsequent (n = 454)	16.04%	7.05%	22.87%	20.26%	21.16%	16.08%	39.93%	56.61%
Ifosfamide 1st wipe (n = 291)	5.84%	6.61%	13.06%	9.69%	13.75%	12.78%	67.35%	70.93%

Subsequent (n = 454)								
5-FU 1st wipe (n = 287) Subsequent (n = 451)	23.00%	12.42%	18.12%	17.07%	14.63%	11.75%	44.25%	58.76%
Overall for all drugs*	10.17%	5.84%	17.37%	12.24%	17.69%	13.56%	54.76%	68.36%

[A]Low Contamination: between 10 and ≤ 100 ng/ft^2 (between 0.0108 and 0.108 ng/cm^2)

[B]Medium Contamination: between 100 and ≤ 1,000 ng/ft^2 (between 0.108 and 1.08 ng/cm^2)

[C]High Contamination: > 1,000 ng/ft^2 (> 1.08 ng/cm^2)

[D]Non-detectable Contamination (ND): ≤ 10 ng/ft^2 (≤ 0.0108 ng/cm^2)

*P-value comparing the overall results for high medium, low and non-detectable contamination levels at 1st and subsequent results is $P < 0.0001$ for all groups.

Table 3: Incidence of contamination for each drug with and without the use of a CSTD								
Drug	**High Contamination[A]**		**Medium Contamination[B]**		**Low Contamination[C]**		**Non-detectable Contamination[D]**	
	CSTD	**No CSTD**	**CSTD**	**No CSTD**	**CSTD**	**No CSTD**	**CSTD**	**No CSTD**
Paclitaxel CSTD (n = 605) No CSTD (n = 137)	2.31%	5.84%	10.58%	17.52%	15.87%	24.82%	71.24%	51.82%
Docetaxel CSTD (n = 605) No CSTD (n = 137)	1.82%	4.38%	6.28%	13.87%	12.23%	14.60%	79.67%	67.15%
Cyclophosphamide CSTD (n = 605) No CSTD (n = 137)	7.44%	24.09%	20.66%	24.82%	17.69%	19.71%	54.21%	31.39%
Ifosfamide CSTD (n = 601) No CSTD (n = 135)	5.32%	10.37%	9.15%	17.04%	13.14%	14.07%	72.38%	58.52%

5-FU CSTD (n = 598) No CSTD (n = 132)	14.72%	26.52%	17.56%	15.91%	12.88%	12.88%	54.85%	44.70%
Overall for all drugs*	6.30%	14.16%	12.84%	17.85%	14.37%	17.26%	66.49%	50.74%

[A]Low Contamination: between 10 and ≤ 100 ng/ft^2 (between 0.0108 and 0.108 ng/cm^2)

[B]Medium Contamination: between 100 and ≤ 1,000 ng/ft^2 (between 0.108 and 1.08 ng/cm^2)

[C]High Contamination: > 1,000 ng/ft^2 (> 1.08 ng/cm^2)

[D]Non-detectable Contamination (ND): ≤ 10 ng/ft^2 (≤ 0.0108 ng/cm^2)

*P-value comparing the overall results for high, medium, low and non-detectable contamination levels with and without the use of a CTSD is $P < 0.0001$ for all groups.